A 4-Year-Old Girl with Gastroenteritis, Anemia, Thrombocytopenia, and Hematuria

Kristina N. Carswell,1 Wafi Bibars,2 Saad Mir,3 Neil Harris,2 and Michele N. Lossius1*

CASE DESCRIPTION

A previously healthy 4-year-old girl presented with a 2-day history of severe nausea, vomiting, and diarrhea. Her symptoms began with diffuse abdominal pain followed by alternating episodes of vomiting and nonbloody diarrhea. There were no reports of sick contacts, recent travel, camping, or unusual food or water consumption. On the first day of symptoms, her primary care physician diagnosed viral gastroenteritis and stool cultures were sent to an outside laboratory. The following day, her vomiting increased in frequency and the diarrhea became streaked with blood and mucus. The patient was taken to a regional hospital where a complete blood count revealed a white blood cell count of 22,500/mL (reference interval, 5.5–15.5 × 10³/µL) with 89% neutrophils and 7% bands. A urinalysis revealed positive ketones of 150 mg/dL (reference value, negative) and a specific gravity of 1.030 (reference interval, 1.005–1.030). She was then transferred to our hospital for management of neutrophilia and dehydration. On admission, her temperature was 38.7 °C, but other vital signs and physical exam results were unremarkable. She was treated with intravenous fluids. Stool cultures for bacteria, shiga toxin, ova, and parasites were obtained. Urinalysis showed positive protein of 300 mg/dL (reference value, negative) and 4 red blood cells per high-power field (reference value, negative). On day 2 of admission, the patient passed cranberry-colored urine. Repeat laboratory test results at this time revealed creatinine of 1.10 mg/dL (97.2 μmol/L) (reference interval, 0.03–0.7 mg/dL), a blood urea nitrogen (BUN)4 of 26 mg/dL (9.3 mmol/L) (reference interval, 6–20 mg/dL), a hematocrit of 30.7% (reference interval, 34.0%–40.0%), and a platelet count of 28,000/µL (reference interval, 150–450 × 10³/µL). Her blood smear is shown in Fig. 1. She continued to demonstrate anemia and thrombocytopenia throughout her hospital admission. Her stool cultures (and blood cultures) sent on admission were negative for pathogens.

DISCUSSION

Hemolytic uremic syndrome (HUS) is defined by a triad of microangiopathic hemolytic anemia (characterized by schistocytes and helmet cells, as shown in Fig. 1), thrombocytopenia, and renal dysfunction. It is a leading cause of acquired renal failure in children in the US. In almost all diagnosed HUS cases there is a preceding diarrheal illness, which defines typical HUS. The most common pathogens causing HUS are Escherichia coli (specifically toxin-producing O157:H7, along with other E. coli strains), followed by Shigella, and finally, a variety of other less common bacterial causes. If the disease is not preceded by a diarrheal prodrome, then it is considered atypical HUS.

HUS presents most commonly in young school-aged children. In typical HUS, the onset of complications occurs 3–7 days (but can be up to 14 days) after the onset of the symptoms of gastroenteritis. These intestinal symptoms may be severe enough to cause hospitalization secondary to dehydration or self-limiting with only mild symptoms. Oliguria due to renal damage can be missed early in the illness because it may be thought to be associated with dehydration from the ongoing diarrheal losses or poor oral intake.

Microangiopathic hemolytic anemia is one of the key features that define HUS. It is characterized by a negative Coombs test despite ongoing hemolysis, and hemoglobin values are generally <8 g/dL. The periph-
eral blood smear can show up to 10% schistocytes, along with helmet cells, which are produced due to damage of the endothelial layer of small vessels, resulting in fibrin deposition and platelet aggregation. As a result, as the red blood cells travel through these vessels, they are damaged and fragmented, resulting in intravascular hemolysis. An increased lactate dehydrogenase concentration is the most sensitive index of ongoing hemolysis. Additional findings include increased indirect bilirubin, reticulocytosis, and a sharp decrease in haptoglobin.

Thrombocytopenia is another component of the triad. Platelet counts are below $140 \times 10^9$/mL but usually stay above $40 \times 10^9$/mL and do not typically lead to clinically significant bleeding. Results of coagulation studies typically remain within reference intervals.

Diagnosis is made by evidence of microangiopathic hemolytic anemia (anemia, thrombocytopenia, and schistocytes/helmet cells seen on blood smear) with some evidence of renal insufficiency. Although the hemolytic anemia may be severe, it does not typically correlate with the severity of renal disease. In typical HUS, a stool culture may be obtained to isolate the most common causes of HUS, *E. coli* O157:H7 should be cultured using MacConkey agar because this particular strain does not ferment sorbitol. Leukocytosis is usually present, but its absence does not rule out the disease. Urinalysis will usually show microscopic hematuria and a small amount of proteinuria. Ketones may also be seen secondary to the catabolic state from general illness. Renal involvement ranges from mild with only slight increases in BUN and creatinine to acute severe anuric kidney failure requiring dialysis.

Complications of HUS include severe anemia from microangiopathic hemolytic anemia, volume overload and hypertension from anuria or oliguria, hyperkalemia from hemolysis of erythrocytes in combination with renal insufficiency, and various other electrolyte abnormalities. Heart failure and arrhythmias can occur secondary to severe anemia and volume overload or depletion. Patients may also exhibit glucose intolerance and transient diabetes mellitus during the acute phase of HUS due to inappropriately low serum insulin. Many patients will present with some form of central nervous system (CNS) disease, including irritability, lethargy, and other nonspecific mild encephalopathic symptoms. Severe CNS involvement is rare, affecting only 15% to 20% of children with documented HUS. CNS symptoms result from focal ischemia to the nervous system from microvascular involvement, which parallels the disease of the kidney. Up to 50% of patients with typical HUS will develop...
On review of our patient’s cultures sent from the primary pediatrician’s office before her admission at our facility, we found that the patient’s original stool culture contained *E. coli* O157:H7 that was positive for shiga toxin, thus confirming our diagnosis of typical HUS.

**Author Contributions:** All authors contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors’ Disclosures or Potential Conflicts of Interest:** No authors declared any potential conflicts of interest.

**References**


While many serotypes of STEC can cause HUS, it is most commonly associated with *E. coli* O157:H7. Other serotypes progress to HUS less frequently but can cause sporadic disease and outbreaks, such as the O104:H4 strain that was associated with the recent German outbreak.

HUS secondary to STEC infection is typified by a prodrome of 3 days of nonbloody diarrhea (with or without vomiting), but medical care is not typically sought until the third day when the diarrhea becomes bloody. Progression of STEC infection to HUS in adults is relatively rare, but approximately 10% to 15% of children with STEC infection will develop HUS. The mean age is 4 years, just like the patient in this case.

A stool culture should be performed for all children with acute bloody diarrhea. Practices for culturing stool vary widely between laboratories, so it is very important that providers confirm that the laboratory will culture for *E. coli* O157:H7 specifically when HUS is suspected. The fastest and most sensitive laboratory method for *E. coli* O157:H7 isolation is plating of the specimen to a selective agar, such as MacConkey agar with sorbitol (SMAC). Most strains of *E. coli* that are commensal inhabitants of the gut ferment sorbitol, whereas *E. coli* O157:H7 isolates do not. Enzyme immunoassays for detection of shiga toxin are available and are used by some laboratories. Although these immunoassays can be helpful adjunct assays, they are not a substitute for direct plating to SMAC. Data consistently show that approximately 10% of *E. coli* O157:H7 will not be detected if the SMAC is not included.

---

**Commentary**

Sheldon Campbell¹,² *

The authors present a classic case of HUS associated with infection by a shiga toxin–producing strain of enterohemorrhagic *E. coli* (EHEC). Several points are relevant to this case.

First, although the common O:157 sorbitol-negative strain of *E. coli* is detectable by culture, culture on sorbitol–MacConkey agar alone is insensitive for shiga toxin–producing *E. coli* due to the prevalence of non-O:157 strains. Either toxin detection with any of several immunoassays or detection of the shiga toxin genes with molecular methods will provide superior detection of the diverse range of EHEC strains.

Second, laboratories that detect shiga toxin by antigen or molecular methods should also perform culture on sorbitol–MacConkey or MacConkey agar to recover the strain(s) for typing, which has major public health significance and may be clinically useful as well in some cases. There is no specific medium for detection of non-O:157 strains of EHEC, but plates can be submitted to public health laboratories, which are equipped for isolation and strain typing of these organisms.

Lastly, it is critical that laboratories performing testing for shiga toxin–producing strains include a statement in the report that antimicrobial treatment of these infections is contraindicated; as the authors state, antimicrobial therapy is associated with increased toxin release and poorer clinical outcomes.

---

¹ Department of Pathology and Laboratory Medicine, VA Connecticut Healthcare System, West Haven, CT; ² Department of Laboratory Medicine, Yale School of Medicine, New Haven, CT.

* Address correspondence to the author at: Pathology and Laboratory Medicine/113, West Haven, CT, 06516. Fax 203-937-3893; e-mail sheldon.campbell@yale.edu.

Received June 11, 2013; accepted June 14, 2013.

DOI: 10.1373/clinchem.2013.202788